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LETTER

Catheter retention as a consequence rather than a cause of unfavorable outcome in candidemia

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Dear Editor,

Candidemia is an important cause of mortality and morbidity in the hospital setting [1]. Central venous catheters (CVC) can be the primary source of fungemia, as a result from external infection of the line. Alternatively, secondary CVC infection can occur during bloodstream dissemination of *Candida* from the patient's intestinal flora, especially during prolonged neutropenia or following abdominal surgery. Removing the CVC seems, in principle, a logical step, as *Candida* biofilms are difficult to eradicate from a foreign body by the sole use of antifungal drugs [1]. However, the literature supporting CVC removal is controversial [2–4]. We hypothesized that inconsistent reports among studies may result from the inability to measure factors that are inherent to the daily clinical practice, but difficult to record, such as the time at which blood culture results are obtained (sometimes post-mortem) and the clinical context which can rapidly evolve from maximal care to care withdrawal.

To test this hypothesis, we analyzed the role of catheter removal in the outcome of 444 adult candidemic patients with a CVC in place from 27 Swiss hospitals (supplemental Table 1), including 158 ICU and 286 non-ICU patients. Risk factors associated with crude mortality were assessed by univariate analyses (supplemental Table 2) and multivariate logistic regression models (Table 1) by using variables that were significantly associated with the endpoint in univariate analyses (cutoff P value = 0.15). We built a first model that did not include care withdrawal decision and post-mortem diagnosis of candidemia as variables (model 1) and compared it to a second model that did (model 2). We also developed a model that excluded patients fulfilling these two criteria (model 3). Modified logistic regression models according to a method by Firth [5] were used to overcome the problem of separation.

Within the whole population, failure to remove the CVC was significantly associated with death in model 1 (OR = 4.65, 95% confidence interval 2.28–9.48, $P < 0.001$). However, when care withdrawal decision and post-mortem diagnosis of candidemia were accounted for (models 2 and 3), this association disappeared ($P = 0.11$). The loss of significance from model 1 to the other models was observed in both ICU ($P < 0.001$ versus $P = 0.09$) and non-ICU patients ($P = 0.03$ versus $P = 0.4$), respectively. The same finding was observed when CVC infection was entered as a co-variable within the models (supplemental Table 3). These data show that failure to remove the CVC can be a consequence, rather than a cause, of death in candidemic patients. Yet, the ability to detect an association of catheter retention with death in models 2 and 3 (accounting for care withdrawal decision and post-mortem diagnosis of candidemia) compared to model 1 was

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Table 1 Multivariate analyses of factors influencing crude mortality in adult candidemic patients

Characteristics[a]	Model 1			Model 2			Model 3		
	All patients			All patients			Patients with a post-mortem diagnosis of candidemia and care withdrawal excluded		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
All patients ($N = 444$)[c]									
Age > median	2.12	(1.30–3.46)	0.003	2.01	(1.21–3.32)	0.007	2.01	(1.21–3.32)	0.007
Liver cirrhosis	2.24	(0.93–5.39)	0.07	2.11	(0.86–5.18)	0.1	2.12	(0.87–5.19)	0.1
Cancer									
Hematological	1.55	(0.69–3.47)	0.3	1.79	(0.81–3.97)	0.15	1.79	(0.81–3.98)	0.15
Solid tumor	1.97	(1.17–3.32)	0.011	1.92	(1.12–3.29)	0.017	1.92	(1.12–3.30)	0.018
Days in hospital >10	1.51	(0.90–2.54)	0.12	1.55	(0.91–2.65)	0.11	1.55	(0.91–2.65)	0.11
Parenteral nutrition	1.86	(1.14–3.03)	0.013	1.94	(1.18–3.20)	0.009	1.94	(1.18–3.20)	0.009
Immunosuppressive drugs	2.52	(1.28–4.94)	0.007	2.44	(1.24–4.79)	0.01	2.44	(1.24–4.80)	0.01
Peritonitis, postsurgical	1.79	(1.02–3.15)	0.04	1.68	(0.94–3.03)	0.08	1.69	(0.94–3.04)	0.08
Severe sepsis/septic shock	6.45	(3.81–10.9)	<0.001	5.23	(3.03–9.04)	<0.001	5.24	(3.03–9.06)	<0.001
Absence of catheter removal	4.65	(2.28–9.48)	<0.001	2.08	(0.85–5.07)	0.11	2.08	(0.85–5.10)	0.11
Factors preventing optimal management[b]									
Care withdrawal				8.06	(0.36–180)	0.19			
Post-mortem diagnosis of candidemia				35.9	(2.03–632)	0.015			
ICU patients ($N = 158$)[d]									
Age > median	2.30	(1.03–5.15)	0.04	2.11	(0.95–4.72)	0.07	2.13	(0.95–4.80)	0.07
Days in hospital > 10	3.18	(1.35–7.49)	0.008	2.85	(1.23–6.58)	0.014	2.87	(1.23–6.69)	0.015

Table 1 continued

Characteristics[a]	Model 1			Model 2			Model 3		
	All patients			All patients			Patients with a post-mortem diagnosis of candidemia and care withdrawal excluded		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Parenteral nutrition	3.53	(1.50–8.35)	0.004	3.44	(1.48–8.01)	0.004	3.47	(1.48–8.14)	0.004
Severe sepsis/ septic shock	8.63	(3.59–20.8)	<0.001	6.56	(2.72–15.8)	<0.001	6.59	(2.72–16.0)	<0.001
Absence of catheter removal	12.5	(3.01–51.8)	<0.001	4.59	(0.78–27.0)	0.09	4.70	(0.77–28.7)	0.09
Factors preventing optimal management[b]									
Care withdrawal				0.17	(0.00–10.5)	0.4			
Post-mortem diagnosis of candidemia				13.4	(0.39–460)	0.15			
Non-ICU patients ($N = 286$)[e]									
Age > median	1.81	(0.96–3.39)	0.07	1.77	(0.93–3.40)	0.08	1.78	(0.93–3.42)	0.08
Heart disease	1.71	(0.88–3.34)	0.12	1.60	(0.80–3.21)	0.18	1.61	(0.80–3.24)	0.18
Cancer									
Hematological	0.99	(0.34–2.85)	1.0	1.11	(0.37–3.26)	0.9	1.10	(0.37–3.26)	0.9
Solid tumor	2.55	(1.29–5.02)	0.007	2.51	(1.25–5.04)	0.01	2.50	(1.24–5.02)	0.04
Immunosuppressive drugs	3.2	(1.27–8.01)	0.013	3.18	(1.26–8.06)	0.015	3.20	(1.26–8.09)	0.014
Enterocolitis, neutropenic	3.31	(1.00–10.9)	0.05	3.06	(0.92–10.3)	0.07	3.09	(0.92–10.3)	0.07
Peritonitis, postsurgical	1.86	(0.81–4.26)	0.14	1.77	(0.75–4.18)	0.2	1.78	(0.75–4.23)	0.2
Severe sepsis/ septic shock	4.97	(2.41–10.3)	<0.001	4.38	(2.06–9.30)	<0.001	4.41	(2.07–9.40)	<0.001
Absence of catheter removal	2.80	(1.10–7.11)	0.03	1.63	(0.54–4.93)	0.4	1.65	(0.55–4.98)	0.4
Factors preventing optimal management[b]									
Care withdrawal				12.8	(0.62–264)	0.01			

Table 1 continued

Characteristics[a]	Model 1			Model 2			Model 3		
	All patients			All patients			Patients with a post-mortem diagnosis of candidemia and care withdrawal excluded		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Post-mortem diagnosis of candidemia				12.3	(0.49–309)	0.13			

[a] Factors associated with the endpoint ($P > 0.15$) were entered in the multivariate models and kept if their *P* value was <0.15 (supplemental Table 1)

[b] By definition, care withdrawal and post-mortem diagnosis of candidemia (blood cultures become positive after death) are fully predictive of death and would not fit a regular logistic regression model. We used a Firth logistic regression model [5] to overcome the problem of separation and fit these variables, thereby illustrating the bias that they introduce if not accounted for appropriately

[c] Model 1 N=444. Model 2 N=444. Model 3 N=403

[d] Model 1 N=158. Model 2 N=158. Model 3 N=130

[e] Model 1 N = 286. Model 2 N = 286. Model 3 N = 273

reduced, because these models include smaller numbers of patients with a retained CVC.

In conclusion, our study points out two clinical characteristics that may be difficult to obtain but can be major confounders in the analysis of candidemia outcomes. Failure to account for these factors may contribute to overestimate the role of catheter removal in the outcome of candidemia and explain discrepant results in the literature.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-017-4737-9) contains supplementary material, which is available to authorized users.

Authors' contributions

OM designed, implemented, and coordinated the candidemia cohort study.

JG, SZ, AI, KB, UF, CO, AC, TB, and OM collected clinical data, together with the clinical investigators from the centers of the FUNGINOS network listed in Appendix 1.

JS, KM, RZ, TB, RF, and JB collected *Candida* blood isolates and performed species identification and antifungal susceptibility testing, together with the clinical microbiologists from the centers of the FUNGINOS network listed in Appendix 1.

JB and FL coordinated the FUNGINOS reference mycology laboratory.

OM coordinated the Data Review Committee composed of KB, TB, UF, JG, AI, and SZ.

LD, VE, and PYB organized the dataset and performed statistical analyses.

LD, VE, OM, and PYB wrote the manuscript with the help of SZ, NK, FL, and JF.

All authors critically revised the manuscript and accepted the final version submitted for publication.

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Compliance with ethical standards

The national study has been approved by the Ethical Committee of the Lausanne University Hospital as the coordinating center.Conflicts of interest
The authors have no potential conflicts of interest to declare.

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